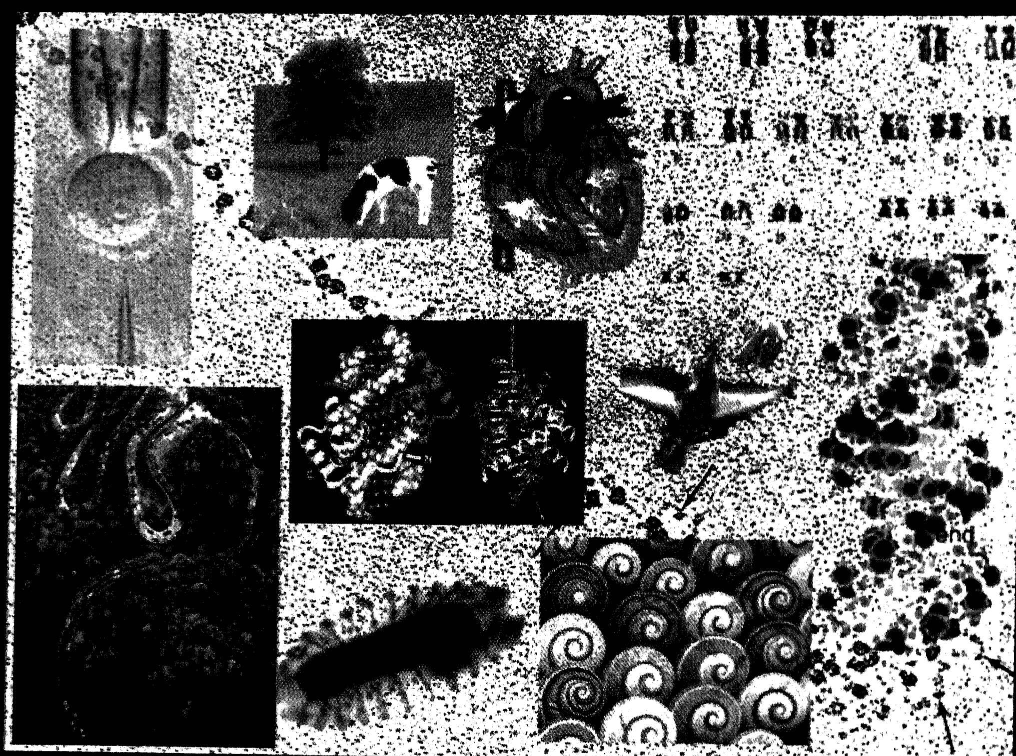
Integrative Biology



Indian National Science Academy
New Delhi

INTEGRATIVE BIOLOGY

INTEGRATIVE BIOLOGY

EDITED BY
S C Lakhotia

Indian National Science Academy
New Delhi

Preface

Biology started as a descriptive science. However, with increasing adoption of experimental approaches in the 19^{th} century, Biology was also as much experimental by the middle of the 20^{th} century as the "Physical" sciences. This encouraged physicists and chemists to also inquire into the nature of life. A turning point in this shift was the small book entitled "What is life" by the well known quantum physicist, *E. Schrodinger.* This and other developments in fields of Genetics and Biochemistry catalyzed the emergence of Molecular Biology, which rapidly became increasingly powerful and popular tool as well as a discipline. As a consequence, the 20^{th} Century witnessed most remarkable and exciting developments in the field of Biological Science. And, this branch of science will continue to dominate at least the first few decades of the 21^{st} Century.

The maddening drive to understand the "molecular" basis of life and the reductionist approach to Biological phenomena resulted in the organismic biology being largely ignored. Specialists were concentrating in narrower and narrower areas of inquiry. As the knowledge in each of the sub-branches of Biology increased, the inter-branch communication unfortunately declined. The biological organism was no more the subject of study, individual molecules and systems gained more importance for the researchers.

As may have been inevitable, after having reached great depths in individual but isolated fields, the need for re-integrating the various sub-divisions of Biology with each other and with other branches of Science began to be felt increasingly, particularly during the past one decade or so. To achieve this integration, the International Union of Biological Sciences (IUBS) has adopted a new initiative named "Towards An Integrative Biology" (TAIB).

Compared to the international scenario relating to teaching and research in Biology, the situation in India remains rather poor. In most institutions of higher learning, rigid compartments continue to debar students from any meaningful inter-disciplinary study and learning. Likewise, a majority of the research programmes in Biological sciences remain confined to narrow fields and consequently, often do not leave much impact. The Indian National Science Academy, New Delhi organized a seminar (13-14 March 2000) on INTEGRATIVE BIOLOGY. The seminar was attended by a large number of

Fellows of the Academy, specializing in different branches of Sciences. Therefore, this meeting provided an excellent opportunity to involve a much wider section of specialists as is required to achieve integration in the broad field of Biology. The basic objective of this meeting was to understand what is Integrative Biology and how can this approach be implemented in our research and teaching programmes. The two sessions on the 13th March were devoted to research while sessions on the 14th March concentrated on Biology teaching.

Integrative Biology is not a new discipline but a philosophy and a mechanism to integrate not only the various sub-disciplines within Biology but also to integrate Biology with other branches of Science in research and teaching. Although integrative biology may have different meanings in different contexts, essentially it aims to incorporate "organismic biology" and "molecular biology" with each other and with other branches of science, conceptually as well as methodologically, so that a holistic view of life processes can be obtained.

The collection of articles that follow are based on the presentations made by different speakers at this Seminar. It is hoped that these will help in dispelling a common mis-conception of a conflict between the so-called "modern" (molecular) and "classical" (organismic) approaches to Biology, which has given rise to beliefs that either of these disciplines can grow only at the cost of the other. This mistrust, however, is unjustified since there is no inherent conflict between the two approaches. It is actually our own mis-placed emphasis on propagation of one at the cost of the other. As has been made clear by many speakers at this meeting, the two approaches are complementary, rather than competitive and a major objective of the concept of Integrative Biology is to bring home the feeling of complementarity.

It is hoped that the academic community and the policy-planners in the country will critically examine the ideas presented in these articles and initiate appropriate steps to bring about the necessary corrective measures in our teaching and research programmes. That alone can stimulate the coming generation of students to study Biology and understand it in a holistic manner so that when taking up research activities, they remain in the fore-front and enjoy the marvels of LIFE.

S C LAKHOTIA
Guest Editor

Contents

Research in Biology: The Role of MRI and *in vivo* NMR along with the Integration of Other Branches of Science in Understanding the Living System

N R Jagannathan
Department of NMR, All India Institute of Medical Sciences,
Ansari Nagar, New Delhi 110029

Biology has undergone tremendous change in its contents and methodology both in research and teaching, in the recent past. This is mainly due to an unprecedented explosion of knowledge during the last four or five decades, which has widened the horizon of science of life. Biology, a discipline of science, has contributed enormously to our understanding of the origin and evolution of life, its continuity and its application in different areas of contemporary frontiers, such as, agriculture, medicine, etc. as illustrated in figure 1. Biology is an indispensable area of human knowledge for physical, social and mental well being. Infact, with the availability of modern sophisticated and powerful techniques, the understanding of life processes at various level has increased. Several behavioural and physiological parameters can be assessed at the level

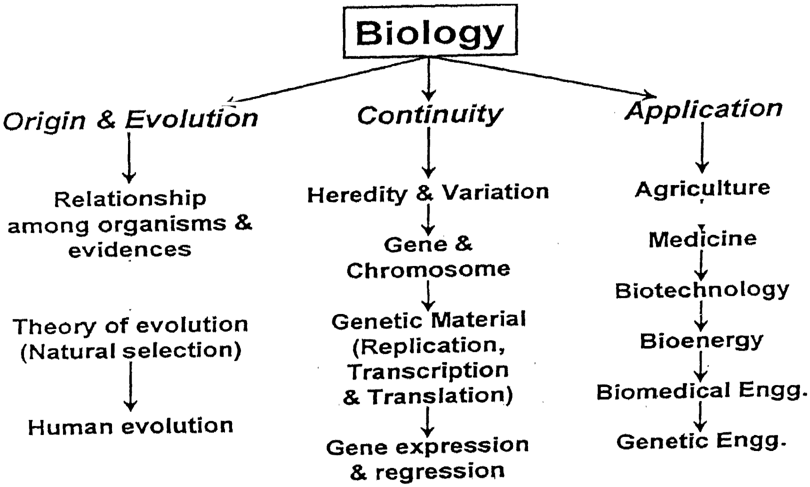


Figure 1 The architectural structure of the application of biology

of whole organism. Besides conventional techniques used to study physiology, modern gadgets range from monitors to measure ultrasonic waves generated by a flying bat to whole body NMR imaging measurements. Using powerful electron microscopes it is possible to study the architectural details of living systems at cellular, subcellular and molecular levels. Biochemistry, a subclass of biology, has infact contributed enormously to the interpretation of myriads of interpretation of life processes in chemical terms. Molecular biology, is another area which has given us the structural and functional aspects of nucleic acids and proteins. Recombinant DNA technique, genetic engineering, etc are other powerful tools to study gene structure and its other functional attributes.

In this presentation, focus will be on a specific aspect of the application of biology, namely, the area of medicine. Since medicine is a vast area, this article will concentrate on the role of Magnetic Resonance Imaging (MRI) and *in vivo* Nuclear Magnetic Resonance Spectroscopy (MRS) technique and how this methodology has helped our understanding of the living systems. It is well known that NMR spectroscopy has played an important role in many areas of physics, chemistry, biology and meterial science (Gadian 1982). NMR is useful to study structure, conformation and dynamics. However, the development of NMR in biology has taken two directions: (i) study of macromolecules, and (ii) imaging and *in vivo* spectroscopy for clinical diagnosis, physiology and metabolism. Magnetic Resonance *in vivo* Spectroscopy (MRS) of cells, organs and tissues in humans and animals, are an extension of the traditional high-resolution NMR techniques applied to more complex systems. It can be used to observe different metabolites present in a particular region and determination of the concentration and relative levels of these metabolites provide information on normal and abnormal state of the tissues and organs and their response to various therapeutic modalities (Ernest et al. 1987). In short, *in vivo* MRS can be used as a unique means for probing the biochemistry of living systems. MRI, on the other hand, is a new state-of-the-art non-invasive imaging modality in diagnostic radiology (Decertaines et al. 1992, Kuchariczyk et al. 1995, Jagannathan and Raghunathan 1995). MRI provides a spatial display of the distribution of nuclei (such as hydrogen) and provides a high-resolution morphological picture (anatomical information) with superior contrast resolution compared to CT scanning. Even though for a number of reasons, MRI and MRS have evolved more or less independently, *in vivo* localized MRS in humans and other living systems, are mainly guided though MR images acquired earlier. Thus, the success of MRI has led to considerable interest in MRS, as a non-invasive probe for monitoring the biochemistry of living systems. Needles to say, that MR has integrated scientists from different branches of science namely, medicine, physics, chemistry, engineering and technology.

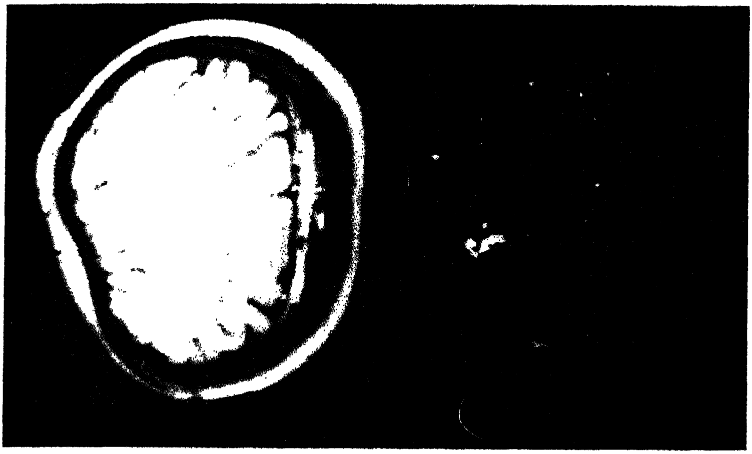


Figure 2 Functional MR image from a study of motor task activation. Image on the left is the anatomy of the selected plane while the right side of the figure shows the effect of activation due to left-hand movement of a volunteer.

Since the area of MRI and *in vivo* MRS is itself vast and expanded tremendously, in this presentation only 2 or 3 examples will be given to highlight in role of MRI and *in vivo* NMR in integrating different disciplines of science which has improved our understanding of the living systems and their processes. Let us first take the recent development in MRI methodology which has demonstrated the possibility of observing human brain functions through functional MRI (fMRI) (Higgins et al. 1997, Stark & Bradley 1997). This technique has great potential for assessing individual pathophysiology and for characterizing different human brain functions such as language-learning, memory, task activation, etc. Figure 2 shows the fMR image from the study of task activation. Anatomy of the selected plane is shown on the left while the effect of activation due to left hand movement is shown on the right (Jagannathan & Raghunathan 1995). Thus, the application potential of fMRI are enormous. This area of research has integrated many specialists from the field of neurosciences such as neurology, neuroanatomy, neurosurgery, and specialists from neural network, computer, statistics and physiology, as well. The second example is in the area of the application of *in vivo* MRS in humans and animals, which has again widened our understanding of the diseases processes at the molecular level, by monitoring the biochemicals (metabolites) in a non-invasive manner. Repetitative measurements are possible because of its non-invasive nature which is useful for follow-up studies as well as to evaluate the efficacy of drugs, in *in vivo* (Decertaines et al. 1992).

The third example is the role of *in vivo* MRS in brain development. Deficiency of thyroid hormone during central nervous system ontogeny, results in a variety

of clinical, anatomical and biochemical defects. Delay in thyroxine therapy in new born with congential hypothyroidism leads to irreversible brain damage. We in our institute, have used localized *in vivo* proton MRS to assess the biochemical changes in different regions of the brain in patients with congenital hypothyriodism before and after thyroxine therapy. A variety of biochemical abnormalities related to myelin maturation were demonstrated and these were found to be reversible on thyroxine therapy. Reversibility was documented even through thyroxine therapy was initiated at ages beyond which abnormalities in myelinogensis are considered irreversible. This research has integrated scientists working in NMR, endocrinology and neurosciences. Similarly, NMR studies of tumors and cancers have brought together specialists from oncology, biochemistry, surgery and radiotherapy, to understand the tumor physiology and its effects (Decertaines et al. 1992).

Thus, the tools of modern biology have permitted dissection of biological phenomena to be interpreted in molecular terms by looking at molecules. Reconstruction and reassembling of these various components is necessary to understand the biology as a whole. Life is not just a conglomeration of cells and molecules but consists of unique events of self assembly, organisation and expression. The precision with which these processes are passed on from parent to progeny ensures continuity. In nut shell, the few examples cited here by the author from this own experience, clearly demonstrate the role of integrating different branches of science to understand the biological processes of living systems, in general.

References

DeCertaines J D, Bouee W M M J and Pado J (eds) (1992) *Magnetic Resonance Spectroscopy in Biology and Medicine* (Oxford: Pergemon Press)

Ernst R R, Bodenhausen G and Wokaun A (1987) *Principles of Nuclear Magnetic Resonance in One and Two Dimensions* (Oxford: Clarendon)

Gadian D G (1982) *NMR and its Applications to Living Systems* (Oxford: Clarendon)

Higgins C B, Hricak H and Helms C A (1997) *Magnetic Resonance Imaging of the Body* (New York: Lippincot-Raven)

Jagannathan N R and Raghunathan P (1995) Task activation of the human brain studied in real time by functional magnetic resonance imaging; *Curr. Sci.* **69** 448-451

Jagannathan N R, Tandon N, Raghunathan P and Kochupillai N (1998) Reversal of abnormalities of myelination by throxine therapy in congenital hypothyrodism: localized *in vivo* proton magnetic resonance spectroscopy (MRS) study; *Dev. Brain Res.* **109** 176-186

Kuchariczyk J, Moseley M and Barkivich A J (eds) (1994) *Magnetic Resonance Neuroimaging* (Boca Raton: CRC Press)

Stark D D and Bradley W G (1997) *Magnetic Resonance Imaging*; Mosby

Integrative Biology: Beyond Dichotomies

M Vijayan
Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560 012

Integrative Effect of the Molecular Approach

During the past half century, biology has been dominated by the molecular approach. It is indeed this molecular approach that brought modern biology to the center stage of science during the second half of the 20th Century. Although it is a highly reductionist approach, it has had an extra-ordinarily high integrative effect on biology as a whole. Before the advent of the molecular approach, the thread that ran through diverse biological organisms such as plants, animals and micro-organisms, did indeed appear very tenuous. However, at the molecular level, all living organisms, despite their mind-boggling diversity, have DNA containing the same nucleotides as the genetic material coding for proteins containing the same 20 amino acids using similar machinery. Of course, the commonality among living organisms extends well beyond nucleic acids and proteins. All organisms are built up of a small number, certainly less than a hundred, of small basic molecules such as a few nucleic acid bases, amino acids, simple sugars and so on. We might call them the molecular alphabets of life, which might have arisen abiotically in the warm primordial oceans. It is the condensation of these molecular alphabets, permuted in different ways, that gave rise to biological macromolecules. There is a molecular logic of life common to all organisms. The way the logic operates is extraordinarily complex, but the logic itself is relatively simple. Furthermore, the unity of biology at the molecular level makes generalizations possible. Physicists revel in generalizations and that is perhaps why biology has attracted so many physicists.

The molecular approach has had an integrative effect not only in relation to present day biological organisms, but also on our understanding of the history of the biosphere itself. The earth is believed to have originated some 4.5 billion years ago. There is evidence to believe that life already existed on earth 3.8 billion years ago. We still do not have a clear idea of the processes that led to the origin of life. It should have been preceded by a period of chemical evolution which obviously must have consisted of, to start with, the abiotic generation of the molecular alphabets of life. A plausible description of this state of chemical evolution exists in terms of the celebrated Oparin-Haldane hypothesis and Urey-Miller type experiments. Analysis of meteorites and

spectroscopic studies on interstellar space suggest that the generation of the basic building blocks of life is a universal phenomenon and not merely a terrestrial one. These building blocks must have then condensed into meaningful polymers, and the polymers and other biomolecules must have come together to form the first self-replicating systems, through processes about which we are still largely ignorant. Chiral selection must also have taken place during the process. The processes through which the first primordial self-replicating cell arose through stages from a racemic mixture of the molecular alphabets of life constitute the least understood link in the evolutionary history of the biosphere.

Once a primitive cell is formed, the subsequent biological evolution can be understood in principle within the framework of Darwin's theory of evolution. Darwin's theory has existed for more than a hundred years; many evolutionary relationships among higher organisms have also been worked out on the basis of fossil records. But it is the molecular approach that provided flesh and blood, and indeed life, to the skeletal framework of Darwinian evolution. During the last 30 years a whole web of evolutionary relationships have been worked out through comparisons of protein, nucleic acid and other biomolecular structures. A family tree of life of intimidating complexity has now evolved through such comparisons. Naturally it is still evolving. Evolutionary relationships among different metabolic pathways and processes have also been worked out. The molecular approach also brought about major changes in the conventional understanding of classification. For example, the current threefold classification of organisms into bacteria, archaea and eukaryotes instead of the old one involving prokaryotes and eukaryotes is a result of the molecular approach. The current efforts to understand relationships among populations using mitochondrial DNA is another interesting example in this context.

Thus, the molecular approach to biology, though reductionist, has been profoundly integrative.

Integration: Not a Problem Unique to Biology

The integration of phenomena at different levels is not a problem relevant to biology alone. As we all know, classical physics reached the zenith of its perfection by the end of the 19th century through the integration of laws of mechanics, electricity and magnetism and the electromagnetic field. However, the placidity of physics was shattered by the advent of quantum mechanics and relativity in the early decades of the 20th century. But, it was soon realized that the three descriptions of nature are not necessarily mutually incompatible. In situations where the Plank's constant can be neglected as very close to

zero, quantum mechanics approximates to classical mechanics. Likewise, in situations where the velocity of light can be considered as infinite, relativistic mechanics approximates to classical mechanics. However, it has not yet been possible to fully reconcile quantum mechanics and relativity.

Trend Towards Integration

The disparity in scales we encounter in physics is much larger than that in biology. Sizes of the smallest and the largest objects physics deals with differ by trillions of a trillion times whereas in biology the difference in size between a biological molecule and a large organism is in the neighborhood of a trillion times. In physics one encounters, at the extreme, objects moving with close to the velocity of light while in biology we encounter only moderate velocities. In biology, the problem lies more in complexity than in scale. Integration from molecules upwards and from organisms downwards is already on in biology.

In my own area of specialization concerned with the structure determination of biomolecules, this trend has been in evidence for years. Biological crystallography is still concerned primarily with individual biomolecules, but different multimolecular systems are also being investigated. Structure determination of whole virus particles has been in vogue for decades. The analysis of the photosynthetic reaction center in the eighties represented the structure elucidation of an autonomous functional multi-molecular assembly. The most significant of the current efforts is to determine the high resolution structure the ribosome. X-ray crystallography, often in conjunction with cryo-electron microscopy, is now progressing from structural molecular biology to structural cellular biology. At another level, our understanding of the effect of molecular processes at the organismal level is steadily increasing. The molecular analysis of genetic disorders, transgenesis, attempts to correlate behavioral traits with genes are all examples of progress in this area. Joint efforts involving different levels of biology and different approaches are now far from rare. Thus, on the whole integration of biology at different levels is progressing surely and steadily.

The Indian Scenario

Coming to the Indian scenario, I believe that the early practitioners of modern biology in the country by and large had a broad outlook of the subject. Although each worked in a specific area, many of them realized the importance of different areas of biology and encouraged practitioners in diverse areas. Since then, there have been occasions to worry if a tinge of parochialism in terms of different areas of biology had not crept into the community. I hope this has been a passing phase. Happily, integration of different approaches at

the same level and of different levels is beginning to emerge in the country. This need to be vigorously pursued and encouraged. It is also important to ensure that the mistakes committed in the past are not repeated. For example, with the advent of molecular biology, for a period of time, support and encouragement appeared to be almost exclusively concentrated in this area. It meant comparative neglect of other areas such as, for example, microbiology and taxonomy, at an unacceptable cost. Prioritization is necessary but it should not lead to near-exclusivity. It is important to ensure a balanced growth of all facets of biology. In any case, there is not all that much good science going on in the country and whatever is good should be supported.

Beyond Dichotomies

I believe that, by and large, integration of biology and of biology with other disciplines is taking place at a normal pace. However, attitudinal problems often caused by hype and sensationalism, need attention. Conflicts make good copy, but not cooperation and harmony. People often tend to think and talk in terms of dichotomies: molecular approach versus organismal approach, nucleic acid versus proteins, reductionism versus holism, heredity versus environment and so on. The members in each pair do not necessarily reflect conflict; they are often complementary. The approach one adopts often depends upon the context and the level of complexity. Quantum chemistry is a good tool to understand the properties of a nucleic acid base, but the way to study the behavior of an animal is certainly not to set up the Schrodinger equation for it and solve the equation. Emergent properties of a complex system are not often best approached using methods appropriate for the study of the constituents. But that does not constitute a dichotomy. Likewise, the presence of a gene for a certain characteristic often constitute only a possibility. The effect manifests only when acted upon by the environment. Here the relationship is actually one of complementarity and not of conflict. Biology often involves the interplay of a plethora of weak propensities and living organisms are truly multi-component systems. Each component and each level of organization have their role in the scheme of things. Almost as a corollary, each area of biology is important and is complementary to other areas. This realization is important for developing an integrative approach to biology.

Integrative Biology: Biological Sciences at the Cross Roads

Anupam Varma
Indian Agricultural Research Institute, New Delhi 110012

During the 20th Century, biological sciences matured from the realm of descriptive science, to that of understanding the biological functions. As the knowledge in each of the sub-branches of biology increased the interbranch communication declined and the researchers became more and more isolated addressing narrower and narrower questions, and in the process of understanding 'molecules' the 'organisms' are being left behind. Fortunately, in the recent years, the need to give equal emphasis to the biodiversity has been felt essential for sustainability. This shift in paradigm requires integrated approach to deal with all levels of biological organization – from molecules to the biosphere cutting across all biological taxa. This can be achieved by bringing together not only the biologists working in diverse areas but also the non-biologists interested in the biological forms and their organization. In other words, a mechanism will have to be developed to facilitate interfacing of diverse disciplines for understanding biological functions at various levels.

Integrative Science

The world has a great deal to learn from the biological forms. For example, insects are the most perfect flying machines. They have perfected the mechanism to navigate through narrow and complex spaces. Understanding of the insect aerodynamics would lead to the development of micro-air-vehicles through collaboration between engineers and specialists in insect behaviour. Therefore, today we have to strive at not just ' integrative biology' but 'integrative science', through the development of a strong band of highly dedicated and motivated scientists interested in challenging problems requiring interdisciplinary approaches.

Human Resource for Cutting Edge Scientific Research

For developing a strong human resource for scientific pursuits, we need to catch and motivate young scientific brains. In the US in year 2000 the top Siemens prize for individuals - $100,000 scholarship – was won by Lisa Harri, a High School student for developing a new method to detect carrier of a gene responsible for cystic fibrosis. Two other high school students won the team competition for their

method of generating computer programmes to store data more efficiently. The Siemens Foundation was created in 1998 to inspire students for taking up science. Our high school students are equally bright and highly capable of developing into competitive and competent scientists for taking up cutting edge scientific research. This can be judged from the excellent scientific projects presented by the students in 'Science Olympiads', and Indian Science Congress

We must ask ourselves a question as to what happens to these young and bright students showing scientific spark at the post-school stage. The spark dwindles, as a career in basic science appears most unattractive offering no opportunities. The new generation coming out of schools today is much better informed than their counterpart of yesteryears. They want challenges and unlimited opportunities for a better future. It is well known that the children of the people in professions like law, show business, medical etc. very often chose to follow parental profession, but not in science – particularly in the recent years. Integrative biology suffers from the same syndrome of not kindling curiosity in the young brains. Firstly, at the school stage, the teachers are not exposed to the breadth of biology to convincingly respond to the searching questions raised by the students. The integration has to start at the school stage for which we must develop a good training program of continued learning for the school teachers. This is essential for broadening the base of teaching science at the preuniversity stage.

Cross-disciplinary Learning

At the graduate level, by and large, our teaching continues to be based on traditional curricula requiring fixed options for disciplines like Botany, Zoology and Chemistry or Mathematics, Physics and Chemistry. This is followed by post graduation in one discipline. Some universities have introduced interdisciplinary courses, but these programmes are mainly structured by adjusting the traditional courses. Integrative biology requires broadening the base of learning biology so that the science graduate has a broader perspective of the questions in biology and would be equipped to develop integrated solutions. Compared to the international scenario, related to teaching and research in biology, the situation in India remains bound by old concepts. In nearly all institutions of higher education, rigid compartments continue to debar students from interdisciplinary study and learning.

Basic and Applied Sciences

In today's scenario there is certainly a need to break the disciplinary barriers, but this should not be construed to mean 'disintegration' of basic science disciplines.

We must come out of the shackles of traditional courses and curricula and encourage cross-disciplinary learning. The Agricultural Universities in the country have adopted the course-credit system where, in principle, a student

has the freedom to choose courses for the major and minor fields of his/her programme of study. A wide range of courses (shown in the outer circle of figure 1) based on the basic core sciences (middle circle of figure 1) are made available for this purpose. It is a good example of integrative biology. The students trained in these universities are well equipped to tackle complex problems related to agriculture and its development. However, at the core lie the basic sciences like Chemistry, Physics, Botany, Zoology, Geology and Mathematics which cannot be ignored for sustained societal progress. The developments in basic sciences

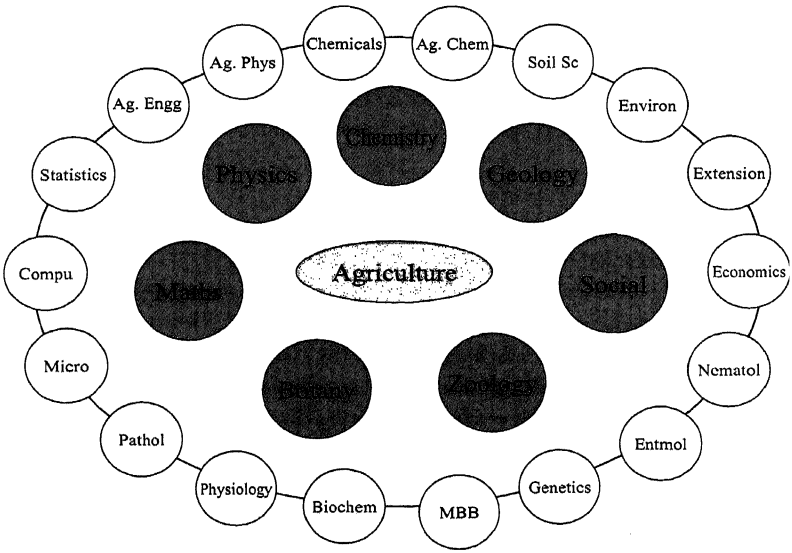


Figure 1 Integrative science teaching in Agricultural Universities. The outer circles indicate the breadth of courses available as options to the graduate and fresh-graduate students. The middle circles indicate the basic sciences on which the optional courses are based.

are life-line for the allied and applied sciences. The basic sciences, therefore, have to be nurtured and nursed with utmost care and support. And, the objectives of integrative biology (or integrative science) have to be achieved through the creation of scientific temper and platform for active collaboration. Such efforts in the present scientific world are common as can be seen by the increasing numbers of multiauthored scientific papers published in leading science journals.

Educating the Integrative Biologists

Tthe integrative biology is not just assimilating and synthesizing total information, but a path of approaching questions and to think broadly about their solutions. The question arises as to how to educate the 'integrative biologists'. This can be realised through:

- Discussion between scientists of diverse expertise on the ways of integrating their approaches.
- Development of teaching aids for 'integrative biology' giving greater breadth of examples.
- Emphasis on the transdisciplinary training.
- Ensuring a broad approach, and to draw analogies between evolutionary and development (evo-devo) studies of plants and animals.

An integrative approach for studies on plant and animals would certainly yield useful comparative information on evo-devo of diverse bioforms. These studies may help in identifying the development constraints that do not allow an organism to evolve into an infinite variety of forms. Molecular technologies would provide important tools for such studies but the new biology would continue to require expert support from basic botanists and zoologists.

Collective Excellence in Science

World over, for historical reasons – particularly World War II, science policies have been mainly led by physical scientists. The twenty-first century will be the century of biological sciences. It is high time for the biological scientists to share the leadership role equally, if not to a greater extent. They must plead for support to all branches of sciences as scientific researches cannot be done in isolation. Excellence would blossom in all the disciplines when equal efforts are directed to bolster basic research in all the disciplines of science so that the biological sciences are not neglected. We have to strengthen research and training facilities to produce leaders in all branches of science in a much greater number to undertake basic and applied research for developing solutions to the emerging complex problems.

Today's science demands teamwork to a much greater extent than at any time in the past. Collaboration is the key for achieving collective excellence in science. The work of one collaborator becomes the input for the other collaborator and so on till the final output is achieved. This requires optimal utilization of available talent and resources. A key factor in this endeavour is the motivation of the scientists. Money does not motivate scientists. They need recognition and the attention of fellow scientists.

INSA as the Motivating Force

The Indian National Science Academy (INSA) plays a key role in the country in motivating scientists. In the twenty-first century, INSA will have a greater proactive role in strengthening the science base of the country, and in realising the objectives of 'integrative biology'. The following suggestions may yield useful results in meeting the emerging challenges to science in India.

INSA may recommend (a) flexibility in science teaching in the universities with greater investment to support basic research in all the disciplines of sciences, and (b) increased support to R & D efforts of the private sector for creating challenging job opportunities. This will help in reversing the current trend of graduate students moving away from science subjects. We have to attract the talented students to science in a much larger numbers.

INSA must continue to motivate all the scientists. During the last two decades biological sciences appear to have been neglected (figure 2). In the twenty-first century the 'hopper-graph' needs to be changed to a 'straight –line' by giving equal attention and recognition to the scientists working in different branches of science.

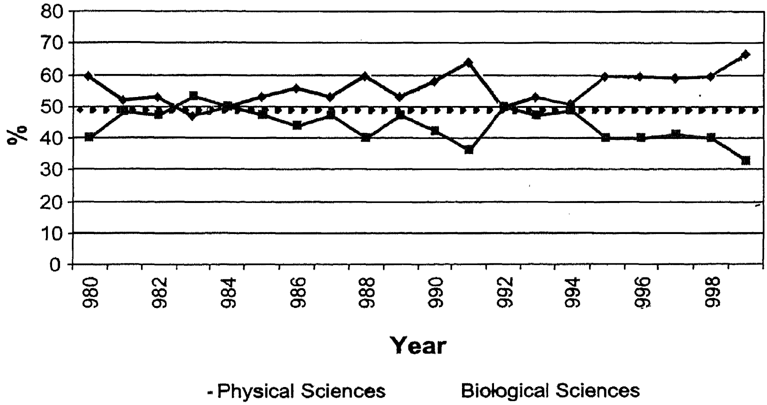


Figure 2 'Hopper'- graph of the percentage of Fellows of INSA elected in Physical and Biological Sciences during the last two decades.

Concluding Remarks

Biological sciences are at the cross roads requiring integrated approaches for understanding biological functions and organization of the myriad of forms. The 'integrative biology' provides interface between science disciplines by bringing together diverse expertise for addressing complex problems of biological realm. We have to train and build a competent human resource not only to lead researches in these areas but also to guide research policy in the new century.

Acknowledgement

The author is thankful to INSA for inviting him to present his views in the symposium on 'Integrative Biology'.

Integrating Biology through Computation

Upinder S Bhalla
National Center for Biological Sciences, GKVK Campus, Bangalore 560065

Introduction

Biology is characterized by complexity and diversity. In the past this has meant that its theories have been qualitative rather than quantitative. Rutherford probably had biology in mind as an example of the 'stamp collecting' variety of science. Indeed, much of modern as well as classical biology is characterized by close examination of special cases. Given the immense diversity of species, of molecular mechanisms and of genetic variations, it could hardly have been otherwise. It may be more accurate to say that this vast exercise in data collection has been a necessary prelude to the application of the sort of quantitative theories that Rutherford presumably would have preferred.

How might the field in general, and Indian researchers in particular, address the task of weaving together the complex strands of life into a meaningful tapestry ? I suggest that computational approaches are a particularly apt solution for the sorts of problems that biology poses. This is of course strongly biased by my own research interests. I will then turn to teaching in the field, and make some rather speculative suggestions about how we might enliven the area to attract and better prepare the next generation of biologists.

Computational Biology as an Integrative Process

There are two key aspects of computational biology:

(i) The use of computation as a tool in doing biology
- Web/communication
- Statistics and analysis
- Instrumentation
- Imaging
- Data management/informatics

(ii) The study of computation as an aspect of biology
- Signaling
- Immune selection
- Genetic programs
- The brain

Of these two aspects, the use of computation as a tool has the potential for being a powerful integrative force. I propose that a key step in realizing this

potential is to develop accurate, predictive simulations of biological systems. In order to develop a successful model, it is not sufficient merely to have the facts in hand. The facts must be quantified and organized in a manner relevant to the model. There must further be an underlying conceptual framework sufficiently rigorous that it can be expressed as equations and algorithms. Finally, the model itself must satisfy the requirements of a good theory: It must advance our understanding of the biological system, and it must pose further questions and predictions for the experimenter.

(a) *Data Quantification and Organization*

Any generic database enforces a certain discipline in data management. This may appear at first sight to be rather trivial book-keeping. The experimental challenges in producing good quantitative data are indeed much more direct and compelling. Nevertheless it is clear from many exercises in developing accurate simulations that the most rigorous-seeming experimental data set is often woefully incomplete. The crux of the issue is that any theory-driven approach is likely to raise questions which may not even occur to an experimentalist. In this way, the value of simulations as a theoretical counterpart to experiments may become evident even before a single computation is carried out. There are also entire disciplines that arise once data is available in a well-designed database. Bioinformatics and genomics are examples of novel fields of inquiry which are based upon, but go far beyond, systematic cataloguing of biological data. It is a common lament of statisticians that biological experiments are rarely planned with proper statistical rigor. This is even more the case when one seeks to build a strong predictive framework - an integrative map of biology - from experiments performed without this broader perspective in mind.

(b) *Conceptual Frameworks*

Biology has several immensely powerful and broad conceptual frameworks. The theory of evolution and the core principles of molecular biology are examples, but so is the now utterly commonplace principle that life begets life. Somehow these lack the aura that adorns comparable theories in Physics. The key ingredient may well be that Newton's laws of motion can be expressed as differential equations, and give rise to precise quantitative predictions. We are not yet ready for a quantitative statement of the theory of evolution, but there is a whole class of biological problems that can and should be posed in a quantitative manner. This typically involves reducing them to questions in chemistry and physics, for which standard quantitative methods apply. This may seem like reductionism in the extreme. On the contrary, it is only by going to the roots of the problem and integrating the other disciplines into biology that one can build a coherent model of complex systems. Many of the problems

that can be posed in this manner are themselves very far-reaching. In light of current knowledge, it seems reasonable to suggest that most aspects of the cellular machinery can be tackled using the conceptual framework of chemical and physical principles and dynamics. The primary difficulty in this has hitherto been the sheer complexity of these problems, but this is precisely where modern experimental biology and computer methods can best be integrated.

(c) ***Good Models***

There is a delicate balance in biological modeling between too little detail and too much. Insufficient detail can hide some of the defining features of a system, whereas too much detail can make it as difficult to understand the model as the original system. There are also constraints on detail due to limited computer power and experimental data. Fortunately, the domain of useful models is large. Indeed, the very overabundance of data that has highlighted the need for integrative biology has expanded this domain. Computer power too has increased enormously. A prime example of this is the proposal by IBM to use brute force computation (the "Blue Gene" project) to solve one of the outstanding biological problems, that of protein structure. The experience of neuronal biophysics and neuronal modeling over the last 50 years illustrates the strengths of numerical simulations in integrating diverse streams of science and biological experimentation with a rigorous, quantitative theory. One could regard a computational description of any problem (not just a biological one) as the final step in fully understanding it. In other words, if you understand something well enough to explain it to a computer, you truly understand it. Understanding of course includes experimental data as well as the theoretical and analytical tools used to make sense of it. The computer in this context is both a data management tool, and a predictive one.

Research Challenges for Integrative Biology

With this viewpoint in mind, I would like to suggest the following as key research steps in understanding biology. In each case the underlying theme is the build-up of experimental data, through the use of ever more sophisticated techniques, till a reasonable computer model can be made to embody much of the available information. Such an approach would exemplify integrative biology.

- Protein structure-function
- Cellular signaling/gene regulation
- The cellular machine
- Development
- Biology of whole organisms
- The brain
- Ecosystems

This list is clearly a project of sufficient scope for many years to come. Which of these research programmes are relevant to the Indian context ? The resources required may seem daunting. The previously mentioned "Blue Gene" project by IBM has a $200 million budget to tackle the protein structure problem through the use of brute force computation of the kind that beat Gary Kasparov in chess. Nevertheless, the Indian experience is that relatively modest investments in combination with intelligent deployment can be highly effective. There is an interesting parallel between IBM's "Blue Gene" and its predecessor "Deep Blue" in the arena of chess. In chess, the closely competitive runner-up, "Fritz", runs on a PC. The difference in resource costs is over a thousand fold.

Computational approaches may be well suited to work in India, given our strengths in the area and relative cheapness of computation. The experimental inputs will always be necessary, but it is hard to see how we could put in the kinds of resources that are necessary for amassing the vast amounts of data required. If one regards data as a commodity, and computational theories as highly sophisticated manufactured products, it might be nice to have a reversal of the usual flow of cheap commodities from developing to developed nations.

Teaching Integrative Biology

Aside from financial limitations, human resources are the primary constraint in developing a new field. Integrative biology has particular difficulties in this regard because of the traditions of our educational system. From my schooling, I would say that there are three main categories of students whose attitudes are shaped by our school system:

- Those who dislike mathematics
- Those who dislike biology
- Those who dislike science in general

These attitudes, if anything, harden during the rigid course of a typical Indian science degree. From this list, there are clearly very few students who could even in principle combine quantitative approaches with biology.

It does not seem appropriate for an inhabitant of the ivory tower of a specialized research institution to comment on possibilities for reform of university teaching structures. I will therefore confine my suggestions to possible approaches which assume a core level of biological training. The first is to increase awareness of the career prospects in the field. The second is to plan a widening of the scope of existing degrees through non-classroom methods.

Careers

The standard goal for the biology stream student has traditionally been medicine. As long as this is the case, those entering biological research or industry will

predominantly be those who could not make it as doctors. It will not be easy to build a revolution in the biotechnological field with this mind-set. It is widely believed that the biotechnology industry, including pharmaceuticals, agriculture, natural products and health care, is poised for a major expansion. For this to occur in India requires that students be trained in modern and integrative aspects of biology. By the same token, students will demand such training only if the career opportunities are seen to be as rewarding as in the current star, information technology. There are many parallels between information technology and biotechnology which could in principle suggest a similar approach to promoting them. Both, for example, require a relatively small number of highly trained individuals in the actual production of the software (or genetic construct) and a huge base of service and support personnel to deploy and support the product. It is in the interests of industry as much as of educationalists to foster an awareness of future careers in biology.

Non-classroom Expansion of Biology Training

Traditional biology as taught in schools and colleges is far removed from the demands of modern biology. The time lag for updating syllabi is many times longer than the pace of change in the field. Even the prestigious biotech programs have a hard time keeping up with developments. While one would like to specify broader based and more current syllabi, there are possible options that could be implemented with very little delay and which would furthermore be much better positioned to track innovations. I will discuss two such options: outsourcing computer training, and Web or multimedia-based supplementary courses for the latest material. These options presuppose a certain minimal computer infrastructure available to degree students.

(a) ***Outsourcing***

The largest single gap in the biology student's expertise is in scientific computing. This does not refer to word processing, for which any diploma course will do. I would point to four main computing skills of use to a scientist: programming, spreadsheet use, networking and hardware. Each of these are individually taught in many of the NIIT-type computer training institutions. There may even be omnibus courses which cover all these basics. Rather than duplicate the expensive infrastructure of these organizations, it may be best for degree programs to recommend a set of outside courses any of which could be counted for credit. One possible way of financing such a scheme could be for universities to enter into reciprocal arrangements with computer training organizations to provide computer instruction in exchange for space and similar institutional resources.

(b) ***Electronic supplementary courses***

Even in the best of worlds, pre-set curricula cannot keep pace with events in a field which is changing as fast as biology. Although India boasts several research institutions which are on the forefront of their fields, these are far too small to train more than a few students without losing their focus. It may be possible to leverage electronic media to vastly extend the scope of advanced courses in the forefront of the field. Using multimedia recordings of specialized topics and an internet or CD-based distribution network, we could reach a much wider audience with little extra effort on the part of the researchers in these institutions. Such lectures are typically taught fresh every year or so in these institutions, and incorporate all the new material in the area, so they cannot be improved upon for timeliness. These courses could act as a bridge between somewhat dated material in the textbooks and syllabi, and the latest developments in modern biology. If produced with care, the courses themselves should go a long way towards rekindling an interest in the field.

Integrative Biology

S Ramakumar
Department of Physics and Bioinformatics Centre
Indian Institute of Science, Bangalore - 560 012

Deluge of Data

Sophisticated developments in the field of biotechnology in recent years have generated vast amount of biological data and much more data is expected to become available in the near future. Examples of biological data include, the complete base sequence of the entire genomes of organisms. The gene sequence of humans amounting to about three billion base pairs will be available within the next few years.

Developments in structural genomics are likely to generate large amount of data describing the three dimensional structures and folding patterns of proteins from several organisms whose genomes are completely sequenced.

Another example of biological data is the expression profiles of thousands of genes during the life span of a living cell. Data about enzyme kinetics, reaction rates and metabolic pathways is also becoming available at a rapid pace.

In the light of these developments, bioinformatics, concerned with extracting useful information from such a rich but massive source of data and providing an explanation for the underlying phenomena (data mining), has become an important discipline for new advances in biology.

Need for an Interdisciplinary Approach

It is increasingly felt that apart from the conventional approaches, ideas and methodologies from physics, chemistry, computer science, mathematics, statistics and engineering need to be applied to an avalanche of new information in genomics and structural biology that poses fundamentally new challenges for biologists. Such efforts will not only contribute to an understanding of phenomena in biology such as protein folding, protein interactions, cellular metabolism, cell organisation, morphogenesis, evolution of species and organisation of species at the fundamental level but also will have practical implications for better human health and well being. Excursions into the realms of biology can in turn enrich the other disciplines.

International Initiatives

Realizing the importance of concerted approaches to understanding biology and to take advantage of such an understanding, there have been efforts in Western countries to bring together researchers working in various disciplines with a focus on analysing biological data which may be rightly called Integrative Biology. Such initiatives have been taken by National Centre for Biotechnology Information, USA, European Bioinformatics Institute, UK, University of California at Santa Barbara, University of California at San Francisco, University of Berkeley, University of Chicago, Princeton University, Stanford University, USA. Information about such efforts are available on the internet as also from articles which appear from time to time in journals such as Nature, Science, Physics World, Chemical and Engineering News, Scientific American etc. (see sources).

Some Possibilities in Integrative Biology

Typical but not exhaustive examples of possible areas of research and development in Integrative Biology are, glassy systems in physics and the protein folding problem, control systems and metabolic pathways, dynamical processes, chaos and evolution, non-linear theories, fractal descriptors and morphogenesis, neural networks and the understanding of the brain, use of the state of the art microscopes for studying single molecules, advanced statistical methods for pattern recognition, gene identification in biology, rational approaches to drug design, massive efforts in structural biology to identify possible folds in the universe of proteins, swarm intelligence and optimisation problems, denovo design of proteins and other molecules with novel structures and functions, learning from biological systems which make complicated natural products so as to be able to synthesis organic molecules in the laboratory in an environmentally friendly manner, computing with biological molecules, study of correlations in biomolecular sequences and evolution, sophisticated analysis of biomolecular structure databases.

National Status (Bioinformatics)

Hence it is pertinent to enquire about the current scenario in Integrative Biology in India and also as to what if any needs to be done to make an impact at both the national and international levels.

The Department of Biotechnology, thanks to its wisdom and foresight has already established the Biotechnology Information System (BTIS) programme. The programme is organised around ten information centers spread across the country and several other sub-distributed information centres. The centres apart from carrying out research and development work in bioinformatics

are providing infrastructural support to research workers in biotechnology for accessing biological databases and sequence analysis. The centres also have been organising workshops and training programmes periodically.

Bioinformatics is traditionally known for the analysis of sequences of proteins and nucleic acids and the prediction of macromolecular structures. However, in the present context, bioinformatics at the national level perhaps may have to be cast into an expanded role so as to bring together people and ideas from several disciplines, be able to handle a wide variety of biological information and make significant and lasting contributions to Integrative Biology in the country.

National Initiative in Integrative Biology, Some Suggestions

It is important to impress upon the government as well as the funding agencies to provide support for inter disciplinary research, development and teaching in integrative biology. For example, integrative biology may be identified as an emerging area for funding and some projects may even be funded in the mission mode. At the university level, special grants, at least as a token may be given for the work of Ph.D. students, registered in cross disciplinary areas with more than one faculty member. Seminars, workshops and training programs may be organized at the regional and national levels. The already existing infrastructure of the bioinformatics centers all over the country may be utilized for this purpose. Extended discussion meetings and visitors programmes where people can work together for a few months and solve some problems as well may be organized. International experts and more importantly, scientists of Indian origin who are working in Western countries (e.g. USA) may be invited to give talks in the field of integrative biology. Opportunities may be provided for Indian scientists to participate in seminars and training programmes abroad in Integrative Biology. International collaborations may be encouraged. It might even become necessary to create new databases and software agents to facilitate integrative biology research in the country. It must be emphasized that right kind of people with the necessary expertise, commitment and interest are a must for the success of the programme. Since research in integrative biology is industrially relevant, industries may also be intimately involved in the efforts in integrative biology at the national level.

Close Collaboration between Theoreticians and Experimentalists

The term integrative biology need not be mistaken only for theoretical analysis and computer modeling which is perhaps a soft option. This is because data in biology is generated only through sophisticated experimentation and any verification of the results of theoretical prediction must be through experimental

work. Hence theoretical and experimental approaches are equally important and must go hand in hand to reap the full benefits of integrative biology. For example, drug design among other things would involve identification of drug targets, combinatorial chemistry, prototype design of drugs, improvement of the drug through design cycles, field trials, toxicology studies, packaging and marketing of drugs and feedback analysis which obviously involve both theoretical and experimental components.

Conclusions

To summarize, efforts in integrative biology at the national level will not only contribute to an understanding of fundamental phenomena in biology but also address at least some of the societal problems such as human health and well being.

The Indian National Science Academy (INSA) which has taken the initiative in organizing the meeting on Integrative Biology can in fact catalyze the process of promoting Integrative Biology research and teaching in the country.

Biology Teaching – Urgent Need for an Integrative Approach

S C Lakhotia

Cytogenetics Laboratory, Department of Zoology
Banaras Hindu University, Varanasi 221 005

Biology started as a descriptive science. However, with increasing adoption of experimental approaches since the later part of 19th century, Biology was also as much experimental by the middle of the 20th century as the "physical" sciences. This encouraged physicists and chemists to also inquire into the nature of life. Non-biologists like Niels Bohr, Max Delbruck, E. Schrodinger, Francis Crick and others dramatically changed the nature of Biological studies. These and other developments in fields of Genetics and Biochemistry catalyzed the birth and subsequent rapid development of Molecular Biology. With an increasing number of non-biologists contributing to our understanding of "what is life", the panorama of biological studies has greatly expanded not only horizontally (i.e., interfacing with other science disciplines) but also vertically (i.e., to deeper levels in biological organizations). The 20th Century witnessed most remarkable and exciting developments in biological sciences. Thanks largely to the progress in Genetics and related basic and applied areas, Biology will continue to dominate at least the first few decades of the 21st Century. The maddening drive to understand the "molecular" basis of life and the reductionist approach has helped unravel many secrets of life and this has opened newer and very powerful ways to exploit the biological wealth. Thus the excitement in Biology is not only from the basic science point of view but also because of the biotechnological applications.

In view of the spectacular success of the molecular approaches in Biology, Molecular Biology has become the "in" thing, which most students want to study and pursue. It may, however, be noted that molecular Biology is, at best, an approach to studying the biological phenomena; it is not as well defined a sub-discipline as fields like taxonomy, ecology, physiology, cytology, genetics and so on. Nevertheless, the all pervasive influence and "glamour" of molecular Biology have resulted in a somewhat skewed emphasis on certain aspects of Biology at the cost of others.

Specialists concentrate in narrower and narrower areas of inquiry. As the knowledge in each of the sub-branches of Biology increased, the inter-branch communication declined. The biological organism was often not the subject of

study; individual molecules and systems gained more importance for the researchers. This resulted in an unhealthy dichotomy between "Traditional" or "Classical" and "Modern" or "Molecular" Biology. The latter places emphasis on "biochemical" or "molecular" reductionist approach to biological issues, often without a reference to the organism. In the midst of euphoria over "molecular Biology", the disciplines that deal with whole organisms have generally been branded as "classical" and, therefore, have often been not only ignored but even looked down upon. The conflict between "modern" and "classical" Biology is apparent in research programs as well as in the teaching curricula.

Conflict between "Classical" and "Modern" Biology Teaching

In terms of the curricula being followed at under- and post-graduate levels, the programs of Biology teaching in different institutions in our country may be grouped as follows:

- Curricula where age-old things continue to be taught (teachers use their own student days' notes!)
- Curricula where only the "latest" is taught, ignoring the basics that are considered "classical" and therefore, unnecessary
- Curricula with generally updated contents and a reasonable balance between "classical" and "modern" subjects

The last category is very rare.

Subjects like Classification/Taxonomy, Morphology, Anatomy etc have often been labeled as "classical" as opposed to "modern" subjects like Molecular Biology, Biochemistry, Genetics, Biotechnology etc. Such "modern-looking" programs have become popular because they tend to fetch better grants and better "respect". There is no denying that the new teaching programs in "modern" Biology have been useful in several respects. But the over-emphasis on "modern" Biology has belittled the importance of traditional Biology departments. A contempt for "classical" Biology has also sometimes been notable in the decision-making and influential quarters. However, it must be noted that the so-called "classical" subjects themselves have not become irrelevant in the present context, but it is the content and the manner of teaching of these subjects that have made them "archaic" rather than "classic". Actually, "classical" should always remain "classy"! To cite an example, taxonomy is one area that has suffered considerably. Lack of competent taxonomists in the country is now being felt in every quarter, especially in relation to assessment and conservation of the biological diversity in the country. In the context of biotechnological applications and threats of intellectual property rights, the country today is in a very disadvantageous position. This sorry state of affairs has come to be primarily due to the continued teaching of archaic information in an unstimulating manner and to some extent

also due to a contempt for taxonomy in the minds of many "modern" Biologists. Appropriate integration of informations available from advances in molecular genetics, developmental biology, evolution, comparative physiology, anatomy etc, can make the field of taxonomy as vibrant and interesting as any other. Therefore, what we need is a change in contents of the so-called "classical" sub-disciplines and change in our attitude and approach to their teaching.

The "glamour" and the supposedly better promise for future, attract brighter students to the "modern" courses. Unfortunately, however, these "modern" courses have been introduced at most places without adequate training of teachers and without the minimal laboratory facilities. Consequently, while the departments and faculty claim "modern", and, therefore, respectable status, the students often learn neither the "classical" ("organismic") nor the "modern" ("molecular Biology") Biology adequately. Disillusionment of students is, therefore, not unexpected. On the other hand, the traditional departments, starved of bright and eager students and of funds are in deep despair. If the teachers also lose their enthusiasm, which is not an unlikely event when grants are limited and eager students are not awaiting in classrooms, such departments enter a degenerative path. Such places fail to attract brighter faculty members also. The decline in reputation of many departments of Zoology, Botany or Microbiology etc in different universities in the country, which once upon a time were considered "very strong" and leading departments, reflects this alarming situation.

Thus in the present situation, while the once "strong" departments are decaying, the new ones are, in most cases, without the basic minimal infrastructure (manpower and material facilities). This alarmingly critical situation needs urgent correction.

Rigid Compartmentalizations Lead to Fragmented Teaching

The rigid compartmentalization in our Biology teaching programs is responsible for producing graduates with a grossly inadequate background in Physics and Computer applications (fortunately, Chemistry is often, though not always, one of the subjects at the under-graduate level). Likewise, students opting for "Physical Sciences" are mostly not exposed to Biology. In addition, the apparently invincible boundaries between the traditional Biology department (like Botany, Zoology, Microbiology etc) cause fragmented teaching of common biological themes. Thus common disciplines like Genetics, Biochemistry, Ecology, Evolution etc are taught in piecemeal manner in each of these departments. As a result, the students often fail to appreciate the commonality between the different biological systems.

Our system debars students from any inter-disciplinary study and learning. Likewise, nearly all of the research programs in biological sciences remain confined to narrow fields without a serious attempt to make an integrated

approach. As a consequence, such isolated endeavors do not make the desirable impact that may have been possible with an integrated approach.

Need for Integrative Biology

During the course of the past few decades, there has been an unprecedented explosion in the knowledge and understanding of biological systems; the range of biological systems has also widened, extending from populations to molecules and atoms. Therefore, it is necessary that a student of Biology today is exposed to a holistic view. To achieve this, the International Union of Biological Sciences (IUBS) has adopted a new program named "Towards an Integrative Biology" (TAIB) to restore balance between the various approaches to the study of living systems and to take advantage of the power of Genetics, Molecular Biology, information technology, sophisticated instrumentation etc to understand life at all levels.

While "traditional" Biology employs specific approaches and techniques to study different levels of biological organization, "modern" Biology places an over-emphasis on "biochemical" or "molecular" and reductionist approach to biological studies, neglecting the organisms and their diversity. In contrast, Integrative Biology seeks both the diversity and integration or incorporation

Integrative Biology is not a new subject or discipline but is only an approach to learn and study the diversity of biological organizations in a holistic manner.

Integrative Biology may mean different things in different contexts:

- Multi-disciplinary or cross-disciplinary or trans-disciplinary approach to include incorporation of Physics, Chemistry, Engineering, Information Technology, Sociology, Economics etc
- Use of diversity of techniques to address a question
- Hierarchical approach (from populations to individuals and from organism to molecules) to questions and techniques

As stated by Prof. M. H. Wake (President, IUBS) "Integrative Biology provides both a philosophy and a mechanism for facilitating science at the interfaces of 'horizontally' arrayed disciplines, in both teaching and research".

Biology in the new millenium needs an integrative approach, an integration within the discipline (intra-Biology integration) and integration between disciplines (integration with other branches of Science). This requires not only a balance between the so-called "classical" and "molecular" Biology but it also requires that students of Biology are not debarred from studying Physical sciences and vice-versa. A modular system of courses that allows enough plasticity in choosing course modules as per interests and requirements is essential to produce new generations of students, teachers and researchers who can fully appreciate and take advantage of the exciting developments in Biology that are awaited in the new millenium.

Integrative Biology – Teaching

H Y Mohan Ram
Dept. of Environmental Biology, Delhi University (South Campus),
Benito Juarez Road, New Delhi 110021

By its very nature, science progresses by spurts of revolutionary discoveries followed by periods of normal science. The history of science has witnessed appearance and disappearance of fashions. In the past 50 years molecular biology has witnessed an unprecedented growth through the integration of several subjects and application of new techniques and tools. Connectedness of life was presumed through the Darwinian concept of evolution by natural selection. The homology of DNA in organisms belonging to distinct kingdoms has ushered in a new understanding of relatedness. Not only the genetic code but the basic molecular mechanisms are the same in the most primitive to the most complex organisms. Above all the pathway from nucleic acids to proteins is a one-way street. Information acquired by proteins is not translated back to nucleic acids.

Biologists are continuously baffled by the enormous diversity that exists amidst fundamental unity. Even more mind boggling is the realization that nearly 99.9% of all the evolutionary lines that once existed on earth have become extinct, emphasizing that evolution is an unpredictable process.

The document "Towards An Integrative Biology (TAIB) Program" 1999 has emphasized that integrative biology is both an approach to and an attitude in teaching and research. The IUBS document outlines the benefits that would accrue by bringing together various disciplines of biology and other sciences, including social sciences. The seminar being organized by INSA has come at a time when a large number of fellows are alarmed by a marked drop in admissions to science courses in colleges and universities. Even two decades ago a few scientists had anticipated that science had been over-sold. Globalization has opened up opportunities in marketing, advertisement and management, causing a mad rush of educated youth to business schools.

Revolution in information technology has also resulted in a race to seek admissions to institutions imparting instruction in computer-based courses. The number of engineers who are unemployed is increasing all over India. In the 23 medical colleges in Karnataka there is a shortfall of qualified faculty by 20–25%. In the state of Rajasthan post-graduate teachers who have spent up

to 20 years are on *ad hoc* jobs and it is reported that in the entire university there are only five full Professors! Why should young persons aspire to go to the university system as persons in my generation did? The only hope one can entertain is the turn of the cyclical phenomenon caused by saturation of specialists. More young people are likely to come to science for its own sake.

With such a dismal scenario, what kind of approach should be taken up in teaching integrative biology at various levels?

There are eminent biologists like Ernst Mayr (1997) who believe that "Even the most traditional branches of biology – systematics, anatomy, embryology and physiology are still needed because all of them are endless unfinished frontiers and all of them are still needed to round out our view of the living world. Each discipline seems to have a golden period, and many of them have several. But even after the law of diminishing returns has taken over, there is no justification for abolishing a discipline that has become classical." For example, classical music still survives inspite of the invasion of several kinds of modern music – unconventional, noisy, rhythmic and body shaking and played under dazzling flashes of coloured lights.

As the present discussion is on teaching, I would like to state what has been accepted broadly as the three main goals of education: to learn to learn; to learn to work and to learn to live.

Traditionally teachers in the past have emphasized teaching. A few outstanding teachers have always succeeded in illuminating young minds by generating excitement. I have personally benefited by learning biology in the garden city of Mysore through wonderful field studies. Presently there are new means of learning which are available outside the classroom to the privileged few. Some being interactive, are attractive to the students. Learning to learn must involve both joy and challenge. Academic rigour at all levels comes from disciplined learning.

Secondary Education

I would like to make a few general observations on biology education in the secondary school level first and then make two specific suggestions about integrative biology at the tertiary level.

Up to class X level, every child must be made aware of the wide variety of microbes, plants and animals in the natural world and develop empathy with them. Tribal and rural children have an amazingly rich knowledge about life in their environment. In general, basic knowledge of the human body and its functions is an essential component of school education. It is amazing how little even educated adults know about human biology. Besides learning about the basic laws of physical world, each child must understand that everything

on earth operates in cycles, that all living things are made from cells, all cells come from pre-existing cells, all life is based on the same genetic code, all forms of life have evolved by natural selection and importantly all life is connected. The facts of birth (sex education) and the basis of sex determination must be learnt to develop a healthy understanding about our place in society. The tenets of personal and public hygiene are never learnt as values from the school curriculum.

Many teachers have expressed that the textual material prepared for the integrated science programmes for Classes VIII – X by the NCERT has not met with the anticipated goal. There are no training programmes to prepare teachers for the task of imparting integrated science. Supplementary teachers' manuals are also needed to ensure proper integration. The present course contents being followed for classes XI and XII needs to be updated and condensed. Regrettably only the course contents of Class XII constitute the subject matter for the public examination. The schools themselves are required to teach and examine students in the course covered in class XI. However, in many schools the students are asked to read the courses by themselves.

The text book preparation committee for classes VIII to XII should have some common members for establishing continuity and coherence. Surveys conducted by research scholars have revealed that to avoid monitoring and supervision of their daily duties, teachers would prefer to join government schools where they draw the same salary and enjoy privileges without responsibility. Teaching in a school is socially satisfying and provides plenty of leisure to pursue other interests/occupations. In making these statements, I am conscious that there are a few teachers, who by their own personal commitment have pursued their goals with a high sense of service. They are exceptions. Several thinkers have suggested that school education be entrusted to the community so that teachers become accountable to parents and are forced to be 'customer friendly'.

In spite of criticisms, there have been serious attempts to periodically revise syllabi and prepare textbooks in science for schools, although the quality of production needs to be vastly improved. It is a pity that the government does not consider expenditure on school textbook production as an investment for attracting students to higher learning. The situation regarding undergraduate education is even more dismal. Most books available are written by individuals motivated by money. Serious students who can afford, continue to use books by foreign authors. Global changes have made no impact on our syllabi. The highly compartmentalized, subject-oriented honours and general degree courses are being continued to suit the needs of senior teachers who are often powerful lobbyists in decision-making bodies. Nevertheless

integrated undergraduate courses in Physics and Chemistry have been started at the University of Delhi and a recent initiative to start a course in Biology has been presented at this seminar by Professor Muralidharan.

Tertiary Education

Two important areas in teaching at the tertiary level in which integrative biology can play a significant role are biodiversity and ecology.

Biodiversity- Biologists have been repeatedly emphasizing that the prosperity of a nation will depend on harnessing of its natural resources through the application of skills and value addition, keeping equity as a guiding principle. The long-term maintenance of the health of an ecosystem is the essential requirement for sustainable development. The reversal of the trend of over-exploitation calls for a serious will to check further loss of biodiversity through action plans.

The teaching of taxonomy, which at one time received high priority, has been woefully neglected. The consequences have been devastating. We do not have experts who can identify and classify large groups of organisms such as bacteria, fungi nematodes, arthropods (especially beetles and other insects), marine organisms including algae; the grasses; palms; legumes; orchids etc. The Rio convention (1992) made a specific recommendation to strengthen capacity building in taxonomy. India has just made a beginning in this direction.

Systematic biology presently includes molecular aspects such as DNA finger printing especially where morphology is unable to provide reliable means of delimiting species or where the identify of a variety of a domesticated organism is to be authenticated for establishing intellectual property rights. Another important ingredient of taxonomy would be to impart education in quantitative studies for establishing the environmental status of organisms according to IUCN criteria. My suggestions at this stage would be to set up a small group to evolve a teaching programme on Biodiversity. I understand that a course on Biodiversity and Conservation has been started at the National Bureau of Plant Genetic Resources, New Delhi.

Ecology (with concerns of environment)– Degradation of the environment and resource depletion are direct results of over population and short-sighted development projects. Although several schools and departments of environmental sciences have been set up, the training imparted is too general and the human resource developed is unable to take up specific action plans. Realizing this, a Department of Environmental Biology was set up at the University of Delhi in 1990 with a focus on biological issues. Owing to present constraints only 7 students are admitted every year after a rigorous entrance

test. They are taught by a faculty of experts drawn from the existing departments in the University and other scientific and educational institutions in Delhi. The Department of Sociology is also offering an optional course in M.Phil. entitled Ecology, Society and Environment.

Current Science carried a perceptive article in February 2000 by Raman, Raghu and Sreenath (Vol. 78: 241-247) which argues "for an environment – based higher educational effort in developing countries, working towards global solutions taking the regional realities into account and the regional initiatives reflecting global realities". This paper has critically examined the current environmental issues and has presented a scheme for environmental employment, integrating environment-related educational efforts. Serious consideration needs to be given to this package.

Integration Started Long Ago

N Sathyamurthy
Department of Chemistry, Indian Institute of Technology, Kanpur 208016

Structure and Dynamics

The integration of biology with physical sciences started more than half a century ago, when Watson and Crick proposed the double helix structure for DNA, Pauling the helical structure for proteins and G N Ramachandran the triple helical structure for collagen to explain the observed X-ray crystallography data.

The combined efforts of physicists and chemists laid the foundation for modern day structural biology. Mathematics was in the background. But already Hardy, who claimed that his mathematics had no use for anything, had demonstrated its use in genetics. Computers have only added to the integration in recent years, translating concepts into tangible results and aiding in visualizing. In addition to *in vivo* and *in vitro* experiments, now we have *in silico* experiments.

More than three decades ago, people like P.O. Löwdin saw the power of quantum mechanics/ chemistry and helped evolve quantum biology and quantum pharmacology. The effect of radiation on biological systems and mutation could already be traced to proton transfer in hydrogen bonds that hold the A-T and G-C base pairs in DNA molecules.

Progressive chemistry departments all over the world (including the one at I.I.T. Kanpur) saw that all of chemistry and biology could be understood in terms of structure and dynamics. Understanding of atomic and molecular structure led to the understanding of the structure of supermolecules, the crystals, be it graphite, diamond or DNA. Supramolecular assemblies that have started drawing the attention in the last decade or so could be understood in terms of hydrogen bonds.

Atoms and Molecules

Atoms in molecules are held together by covalent bonds and all of intramolecular motions result from stretches and bends of these bonds. Much before detailed electronic structure calculations could be carried out for large molecules, G.N. Ramachandran pointed out that preferred conformations of peptide molecules were confined to certain portions of the (Ψ, ϕ) space, where

Ψ and ϕ refer to torsional angles. The book on molecular orbitals in Physics, Chemistry and Biology by Löwdin and Pullman was published in 1964. Detailed molecular modeling followed, thanks to the developments in computer hardware and software and graphics capabilities. The result was the software packages like CHARMM and AMBER, developed by Karplus and coworkers at Harvard University and Kollman and coworkers at the University of California, San Francisco, USA, respectively. It is worth adding here that Karplus used to study atom-diatomic molecule dynamics before embarking upon the study of protein dynamics. In other words, detailed understanding of elementary systems paved the way to comprehension of complex systems.

Intermolecular Interactions

Understanding of intermolecular forces holds the key to understanding of how atoms and molecules come together and form liquids and solids and also how chemical reactions take place. The weakest interactions are of the van der Waals type. They are of the order of 1 kcal/ mol or less and they form the basis of all hydrophobic interactions. Almost every atom in a molecule has some van der Waals interaction with a large number of atoms in the molecules in the neighbourhood. Although small in magnitude, they are large in number in large systems, pushing the cost of computation high.

Hydrogen bonds in comparison are much stronger (~5kcal/ mol) and much more directed. Be it in holding the base pairs in DNA or in holding the molecules together in the nectar of life, water, the hydrogen bonds hold the key to life.

Hydrophilic and hydrophobic interactions are much weaker when compared to the covalent bonds (~100 kcal/ mol), but are much more difficult to compute with accuracy, even today. The pioneers, of course, did not wait for fancy computers to arrive. They went ahead and estimated them, based on the available thermodynamic data.

Linear versus Nonlinear Dynamics

Once we know the forces that are operative, it is not difficult to study the dynamics, particularly if we are satisfied with representing atoms as particles and solving Newton's equations of motion. Until the end of the twentieth century, people were content with studying linear dynamics, because that was easy and doable. Thanks to the computers, efforts have been made to solve nonlinear equations and understand nonlinear phenomena.

As early as 1920, Lotka had proposed nonlinearly coupled differential equations that would account for prey-predator relationships. In an open system consisting of infinitely large amount of grass, deer would multiply merrily until they are devoured in number by the tigers, who get their family

growing with the result that the deer population would go down and so will the tiger population subsequently. There are no chemical examples known till this date that follow the Lotka oscillator model. More complex oscillations were discovered in the later half of the 20th century. Belousov-Zhabotinskii oscillatory reaction became the buzzword and spatial and temporal oscillations began to be understood. The reason for interest in these oscillations is not hard to seek. If we could understand them, we could understand the functioning of biological clocks and biorhythms. Superimposed on the oscillations were reproducible noises that could be analysed in terms of deterministic chaos and fractals. Today we know that healthy heartbeats are not as regular as they were thought to be. What we have illustrated above is an example of integration of nonlinear oscillators (physics) and chemical kinetics to understand biological processes.

Flexibility is the Key

Biological systems are complex systems, which are more than the sum of parts that constitute them. Understanding of the behaviour of such systems is possible through an integrated approach of chemical, physical and engineering sciences using computers as practical tools. Therefore it is not surprising that the flexible credit-based education in the United States of America produced a large number of successful biologists although many of them started their careers as non-biologists.

In India, somewhat flexible curricula exists in the IITs and several of the IIT graduates have gone on to study biology. In IIT Kanpur, for example, there are a large number of students enrolling for courses like Biosystems and Basic biological chemistry. The need of the hour is more biology courses and the flexibility to move across traditional barriers. After all, one thing that we can learn from biology is **ADAPTATION**!

Transition from Classical to Molecular Biology: Need for Greater Integration

H K Jain

40 Suryaniketan, Vikas Marg Ext., Delhi 110092

Biology would not have advanced to its present stage without integration with other sciences. Some of the obvious examples of such integration can be seen in the study of biochemical reactions in the 19th century. Important physiological phenomena like respiration and photosynthesis could be understood only in terms of chemical transformations. Also, the mechanisms of sexual reproduction so central to biology were first understood with the advent of microscopy in the 17th century. A controversy raged for a long period between two groups of biologists – the ovists and the spermists. The controversy was set at rest when Hertwig demonstrated convincingly in 1875 the occurrence of fertilization in animals, followed by a similar demonstration in plants by Strasburger .

Interdisciplinary Origin of Molecular Biology

The process of integration has continued to intensify and a stage was reached in the early 1950s when a number of disciplines came together to give rise to the birth of molecular biology. These included genetics, biochemistry, biophysics and microbiology. The starting point of this synthesis resulted in the discovery of the structure of DNA which had been identified in the 1940s as the genetic material. The discovery marked a turning point for biology opening floodgates of new findings of immense significance for medicine, agriculture and industry. In 1994 a Symposium was organized in Chicago to celebrate the fortieth anniversary of the discovery of structure of DNA and the biomedical revolution which followed from it. The proceedings* of the Symposium (Donald A. Chambers (ed.) 1995. The Double Helix Perspective and Prospective. The New York Academy of Sciences, New York, XV + 472) document these advances.

New Opportunities for Assimilation

The determination of the structure of DNA and the discoveries which followed have opened up unparalleled opportunities for a new kind of assimilation and synthesis in biology. For the purpose of the present symposium on integrative biology it is this new synthesis which is of great interest. Increasingly over

the past four decades traditional biology has been transformed with continuing application of molecular techniques giving rise to what many scientists call the new biology. This should be clear from a study of the present day scientific journals whether they be in the field of morphology, physiology, systematics, ecology, pathology, entomology or evolution. The present generation of scientists in all these and other disciplines of biology take recourse to molecular tools and techniques in the course of their research. These developments are also having a profound influence on the teaching of biology. Students enrolling for various courses are exposed to new biology which integrates the classical with modern. Also, they are taught molecular techniques in their practical classes as early as the secondary school and the undergraduate level. For them the distinction between classical and modern biology has little meaning for they receive their instructions in integrated courses.

India's Response

The transition from classical to modern biology has not been uniformly achieved in all countries. Many of the developing countries have lagged behind. This is particularly true in the teaching of biological sciences. It was mostly in the late 1970s that the university system in India took notice of the important developments in molecular biology. The response by and large was to set up separate Departments of Molecular Biology in selected universities. This was done in recognition of the fact that the country simply did not have the human and financial resources to introduce major courses in molecular biology in the traditional Departments of Botany and Zoology in all the universities. A comprehensive approach would have required a large number of teachers trained in molecular biology and a retooling of the existing laboratory infrastructure.

The policy decisions to organize molecular biology courses in selected universities have served a useful purpose. The country now has a good number of highly trained molecular biologists. They are active in teaching and research and many of them are contributing to the development of modern biotechnology in the country in the field of medicine and agriculture. However, the university system at the same time continues to produce hundreds of graduates and postgraduates every year in classical botany and zoology with relatively little training in techniques of molecular biology. Their future must be a matter of concern. They are lost to modern biotechnology industry and their value as teachers will diminish in the years to come. The country can ill afford the potential loss of this vast manpower.

Need for New Initiatives

The important question which this symposium must address is what steps we should be taking at this point of time so that the teaching of fully integrated

modern biology courses can be accelerated in our educational institutions. Basically, three kind of initiatives are needed at present for India to catch up with the developed countries in the teaching of biological sciences.

One Time Catch up Grant

The University Grants Commission should find funds to upgrade the laboratory infrastructure of the traditional Departments of Botany and Zoology so that they are fully equipped to train students in the molecular techniques of biology. The funds should also enable the universities to take up a massive programme of retraining of teachers in the new techniques of molecular biology. International funding agencies like the World Bank, UNDP and UNESCO should be approached for this purpose. The Indian Council of Agricultural Research has already negotiated a soft loan with the World Bank for the development of human resources in the State Agricultural Universities, specially in fields like biotechnology.

New Course Curricula

New national course curricula should be developed for the teaching of biological sciences in our schools, colleges and universities. The revised courses should be based on the concept of integration of advances in molecular biology into classical biology. One or two examples should illustrate this point. Teaching of systematic botany or zoology should take into consideration the additional criteria of DNA sequence polymorphisms. Similarly, teaching of evolution is greatly facilitated if reference is made to the conserved DNA sequences across the different species of plants and animals and to amino acid substitutions in important protein molecules. The concept of molecular clock makes it even possible to determine the period separating evolutionary lines giving rise to different groups of species. Again, teaching of morphogenesis, development and differentiation requires that the concept of gene regulation and homeobox is integrated with the classical approaches. It is not true that students are no longer interested in subjects like systematic botany and zoology and in morphology. These subjects will see a rebound once we begin to teach students fully integrated courses.

M. Phil Conversion Course

A third initiatives is needed to retrain those M.Sc. and Ph.D. graduates who have obtained their degrees in the last thirty years without much exposure to the techniques of molecular biology. For this group of students, a one year M.Phil course in molecular biology with emphasis on practical work should be organized. This course should help to convert this large body of classical biologists into those with a full understanding of modern biology. Fortunately,

the country now has a large number of institutions which are well equipped to offer such a course.

Conclusion

Classical biology has been transformed in the last fifty years with the assimilation of advances in molecular biology. In much of the Western world students are now taught this new, modern biology. In India the process of assimilation has been incomplete with the result that our students of biological sciences remain at a disadvantage. The paper proposes a series of initiatives for our university system to catch up with the developed countries in its teaching and research programmes of biology so that our students become internationally more competitive. They must be exposed to the excitement of the powerful DNA technology whatever be the nature of their courses in biology. This alone will bring them back to systematics and other forgotten disciplines.

Biophysics: A Major Link for Integrative Biology

Girjesh Govil

Tata Institute of Fundamental Research, Mumbai 400005

The fact that living systems are governed by the laws of Physics and Chemistry was recognized way back in the 19th Century. Physicists in the previous century have been fascinated by the way living systems work. While traditional biologists from this period were trying to classify living species based on their morphology, physicists and chemists were trying to give a more unified approach to life. Their attempts were based on the structures of biological molecules and basic biochemical reactions, which have remarkable similarity in all living systems. Thus, while the conventional biologists worked on classification of living systems, some of the world's most distinguished physicists attempted to look at the universality. In our own country, Jagdeesh Chandra Bose was among the first who devised physical methods to study electro-physiology of plants. Well known names in physics and chemistry such as Erwin Shrodinger, Linus Pauling, Max Perutz, Lawrence Bragg, James Watson, Francis Crick and G.N. Ramachandran were among those who laid the foundation of a multi-disciplinary science known as biophysics, which uses laws and tools of physics to understand biology.

The work of Pauling and Perutz helped us to understand that proteins have a well defined three dimensional structure. Early work on hemoglobin, which is not a simple protein, helped in understanding how it delivers oxygen to tissues in a controlled and efficient fashion and led to a sub-discipline called bio-inorganic chemistry. It was the interpretation of the X-ray diffraction data by Watson and Crick, which led to the birth of a new field, known as "Molecular Biology". The work of Prof. Ramachandran helped to understand how proteins fold. The field of biochemistry itself has drawn inspirations from contributions from biophysicists. In many laboratories in the world, there are common departments of biophysics and molecular biology.

Tools in physics allows one to look at the chemistry of living systems at three levels. At the molecular level, the three dimensional structures of molecules of life, proteins, nucleic acids, lipids and polysaccharides help to understand their function. Inter-molecular interactions through weak forces such as van der Waal interactions and hydrogen bonding lead to complex multi-molecular assemblies such as ribosomes, chromosomes, cell membranes etc. It is now known that in order to

carry out biological functions, atoms which constitute biological molecules have to move in space and time. Therefore, one should understand the dynamics of these molecules. Most of our current information on the structure, interaction, dynamics and function of biomolecules has come from X-ray diffraction, NMR and fluorescence spectroscopy. These are every-day tools not only for physical chemists but also for molecular biophysicists. Theoretical techniques such as molecular dynamics, which uses Newton's laws of motion for the movements of atoms in a molecule, help in simulating such events in real time. Today, we know many aspects of biochemical reactions at molecular level and can simulate various steps involved, in real time. Every year almost 700 new three dimensional structures of biological macromolecules are deposited in the data bank for macromolecular structures. From such structures, we know a great deal not only as to how enzymes function, but also some of the more complex and important steps of how a DNA molecule makes its own copy (replication), how the information is transcribed on a RNA molecule and how it is translated during the synthesis of specific proteins.

The next set of applications of biophysics is at the level of cells. Sophistication in microscopic techniques has led to investigations of cell morphology at nanometer resolution. One of the most crucial steps in cells is the bioenergetics; in particular, how ATP is made and how it is utilized. Already, valuable insight on this important event has been reached by biophysicists. Chemists learn equilibrium thermodynamics as a part of their curriculum. However, they have to modify their ideas while dealing with a non-equilibrium situation which exists in biological systems. With advances in cellular biophysics, we know how cell communicate and how signals are transmitted for example, during a neural impulse. What is the difference between a normal and cancerous cell. What are the optimal conditions to store a cell line. And how are cells damaged by environmental factors such as ionizing radiation.

Finally, one would like to know how complex living systems and organs function. Possibly the most complex of these is the human brain. In the last decade, there has been a revolution in what we call functional imaging using diverse physical techniques such as, NMR, optical methods and PET. The methodology involves mapping of chemical changes in specific locations, as small as 1 mm cube of brain when a particular function is being done. Through such studies, we are able to answer questions such as how brain learns languages. What part of the brain is involved in a particular functional activity, for example vision? Is there a difference in the learning abilities of a man vs. a woman for different functions? For example, is there a gender bias in learning of fine arts, science and mathematics?

Once we understand how living system do their functions, we can do two things. One is to modify and make them more efficient. The second is to

control abnormalities. This has direct implications in medical sciences. One of the important area which has flourished in the last three decades is that of drug-design. We may be able to use biological molecules to sense presence of small amount of other molecules such as glucose, urea.

The huge amount of the information which is generated by molecular biologists and biophysicists needs a more efficient management. This field is called Bioinformatics; collecting information and making it available to the user through web-site, where one can have access to sequences of proteins and nucleic acids and the three dimensional structures of biological molecules. For this, biophysicists use tools in computer science. One of the parallel developments is whereby biology can help computer scientists to learn from the neural networks in brain to develop faster computer programs.

Some of the examples discussed may have convinced you that biophysics is one science which has interfaces with all disciplines. A question that is often asked is as to where do we go from here to the next millennium. I shall give you a few examples of things to come. Availability of synchrotron sources, nano-scale diffractometers and methods of direct phase determination have made it possible to study structures of fairly complex biological molecules even when there are difficulties in crystallization, in very short time. This has also led to the birth of time-resolved crystallography where one can follow the course of a chemical reactions on a millisecond time scale. Of course, NMR appears to be a better technique to see how a bond is broken and new bonds formed when a substrate binds to an enzyme and get transformed into the products. Laser based spectroscopy allows you to go to an even lower time scale, that of femto second spectroscopy. Indeed, this year's Noble Prize in Chemistry has been awarded for studies in the reactions pathway of small molecules. It is a matter of time, before such studies can be done on complex biological systems. A great deal has been learnt about cellular morphology and functions in the last 50 years and with new developments in microscopy, much more is to be learnt. The whole range of electromagnetic radiation is used for imaging and spectroscopy of brain and other vital organs. Possibly in the next decade, we should be able to learn through new developments in biophysics, more about the human brain than what we have learnt in the whole of the 19th Century. We may be able to device sensors for taste and smell. And may be we can use biomolecules to make molecular chips for computer memories, reducing the size of the chips almost thousand fold. These developments have given birth to a new science called molecular electronics.

It is rather unfortunate that in spite of the pioneering work of Prof. G. N. Ramachandran and J. C. Bose, there are only a handful of departments in our

country which are devoted to teaching of biophysics. One of the reasons may be that rich schools in biophysics in India are mostly located in research Institutions rather than in the University system. Teaching of biophysics is therefore restricted to what one learns as part of the courses in molecular biology and biochemistry. Unfortunately, this teaching has led students to believe that molecules are static, look colorful, and all that you need to know is to learn their basic structures. In medical schools imaging techniques are taught as a part of radiology, with very little emphasis on basics of imaging and techniques. With the need to learn mathematics, computer science, physics, chemistry and biology, students coming from either the Physics, Chemistry, Mathematics or from the Biology, Chemistry, Medicine background avoid learning of this multi-disciplinary science. There have been at least two committees of UGC which have looked at the problem and have given suggestions, but no meaningful results have come out. Possibly, the best way is to include biophysics as part of a two semester course of integrative biology. One of the associated problems is that unlike biochemistry, there are very few text books world-wide dealing with biophysics at the first level. The advance level books are only for the specialists. This problem has been realized even by the world body dealing with biophysics, namely the International Union for Pure and Applied Biophysics. I feel very happy to announce that recently I had the honor to release the book written by Prof. P. S. Narayanan of the University of Mumbai, on "Essentials of Biophysics". This is among the handful of the first level introduction to students to the field of biophysics, world-wide. I hope this book will be displayed soon on the IUPAB web-page. I understand that the book is only one half of the original text that Prof. Narayanan wrote, simply because the publisher felt that a thicker book due to higher costs will cut down its sale.

If we look for the future of chemistry and physics in the next century, it is indeed clear that it belongs to the scientists trying to understand life. Indeed, the barriers between disciplines are fast disappearing and if you look at the Noble Prizes given in the last 50 years, almost 25% of those in Chemistry, Physics and Medicine have gone to scientists associated with biophysics.

Teaching of Biology in Medical Curriculum

S S Agarwal

Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226014

"Understanding and management of human health and disease in modern scientific medicine is intricately dependent on the knowledge of human biology".

In our country after qualifying 10+2 in Physics, Chemistry and Biology, students are admitted to medical school. The Graduate programme in medicine is of 4½ years duration which consists of 2 semesters of training in Anatomy, Physiology (including Biophysics) and Biochemistry (including medical physics and molecular biology). This lays down the foundation of normal structure and function of human body. Further training in Pathology and Microbiology provides frame work for understanding alterations in structure and function which are responsible for disease. The training in microbiology also provides exposure to structure and function of microbes and host-microbe interaction which includes immune response to invading organisms. As part of Pharmacology medical student is taught about targets and mechanism of drug action, structure – activity relationship of the drug molecule, as well as metabolism of drugs. The training in these 3 subjects viz., Pathology, Microbiology and Pharmacology spans a period of 3 semesters. On the clinical side too, which comprises remainder part of the training, reference is regularly made to structure and function of the affected organ of body to understand clinical presentation and to have a scientific basis for investigations and their interpretation. The ultimate goal of therapy is to restore the structure and function to normal as far as possible.

Thus, the entire training of modern scientific medicine is centered on human biology though the term biology as such is not mentioned in the medical curriculum. However, it is also true that in actual practice of medicine, which largely consists of (1) history taking and physical examination, (2) ordering of investigations and interpretation of results, and (3) prescribing of drugs or conduct of non-surgical / surgical interventions, to ameliorate the disease, the knowledge of biology does not appear to find direct application. The attitudes, the skills and the practices occupy much more important place in the practice of profession; even though the knowledge (which is based on the understanding of human biology and pathobiology) is the driving force in decision making and competence. The need for good understanding of biology is critical for medical teacher and researcher.

The watch dog body for laying down and maintaining standards of training in modern scientific medicine in the country is the Medical Council of India. It has revised the graduate medical curriculum in 1997 which has been published as 'Regulations on Graduate Medical Education' in the Gazette of India on 17th May 1997. It is an excellent document which clearly lays down overall goals and specific contents for knowledge and skills in each subject of graduate training programme in considerable detail. Selected statements relevant to the present discussion from this document are included in the Appendix. However, one does not know how much of it, and of what quality, is actually translated into action by all the medical schools across the country. One would need to examine 'question papers' and scores obtained in specific areas by the students to address to this question.

Although, the subjects of Genetics, Immunology do not figure in the list of the MCI as such, yet there is sufficient incorporation of molecular and genetic concepts in the prescribed curriculum of Biochemistry and other subjects to provide for training and evaluation in those areas. The only drawback that I can find in the curriculum is that training in these areas is not linked to training in the clinical subjects. With successful completion of the Human Genome Project it is envisaged that genes will become known not only for all the genetic disorders but also for polygenic multifactorial disorders like Diabetes, Hypertension, Coronary Artery Disease, Obesity, Behavioural disorders etc etc. It may be possible to screen and identify individuals at risk much before the onset of the disease and to take appropriate steps to prevent its occurrence (Predictive Medicine). This would require knowledge of availability, applications and limitations of various DNA diagnostic tests by all practitioners of medicine, irrespective of their specialty. This would also require redefinition of clinical presentation, pathobiology, investigations and management at molecular level, the so called Molecular Medicine (figure 1).

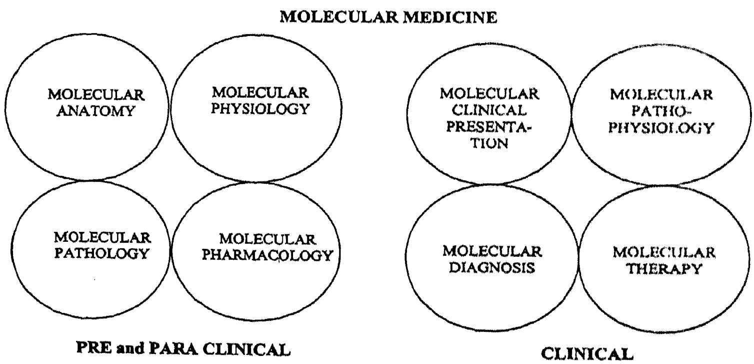


Figure 1

The Graduate program consisting of 4½ years of medical education and training and 1year of internship is aimed to train a Basic doctor (M.B.B.S). The Basic doctor is expected to 'undertake the responsibilities of a physician of first contact who is capable of looking after the preventive, promotive, curative and rehabilitative aspects of medicine'. This responsibility includes identification of problems which need referral and appropriate guidance for the same. The curriculum has laid emphasis on a broad base of training to enable a Basic doctor to choose career from a wide range of options, but this has also made the curriculum some what superficial and unwieldy. With explosion of knowledge in all areas it is necessary to define core and optional areas.

The basic training is followed by specialization (MD/MS) and super specialization (DM/MCh) in various branches of Medicine and surgery. Each of these courses is of 3 years duration. The Postgraduate regulations of MCI are rather old (1988) and not so exhaustive as the graduate curriculum which has been recently revised. However, at least in some super specialties, the professional societies have done an excellent job of defining the curriculum which has been voluntarily adopted by most of the universities. While details of these curricula are not known, it must have a strong emphasis on biology since tertiary medical care is heavily dependent on precise delineation of structural and functional abnormalities and their restoration to normalcy. One of the lacunae, however, is that in postgraduate medical education there is very little formal education. There is a need to look into this area by the Medical Council of India.

While the provisions in the graduate curriculum have sufficed for most of human resource development in medical sciences until recent past, the current developments in the field of Human Genome, and in the realm of physical (information technology, imaging technology, robotics), chemical (biomaterials) and mathematical (theory of chaos and non – linear dynamics) sciences, with applications to biology, do require a re-examination of the training programme. I do not think that the prescribed curriculum requires a change. What is needed is the creation of awareness and training of medical teachers in basic principle of genetics, DNA testing and genetic counselling, so that these aspects are included in the teaching programme. The concrete goals of this learning would need to be defined and incorporated in evaluation of students, both in the certifying and qualifying examinations for higher education.

As mentioned above the research in biomedical sciences is heavily dependent on clear knowledge of biology. In recent years the paradigm of 'cell' as the basic unit of health and disease has shifted to 'molecule' as the basic unit of life. A student has to be familiar with not only the 3 dimensional structure of the molecule, but also the mechanisms and consequences of interaction between

molecules (ligand and receptor, transcription factor and the target DNA etc.) which not only requires knowledge of biology, but also of physics, chemistry, mathematics and engineering. Considering the needs of training of a future biomedical scientist, the Manipal Academy for Higher Education has carried out an exercise to evolve an integrated 3+2, 5 year course of M. Sc. in Biological Sciences. Its rough outline is given in figure 2. This provides for training in modern biology as well as specialization in known areas of sciences which have become identified with various job opportunities over time. Unfortunately due to paucity of funds this course has not yet been started. It may be worth initiating such a course at few selected centers in the country.

Proposed 3 + 2 (5 Year) Integrated M. Sc. Course in Biological Sciences as Evolved by the Manipal Academy of Higher Education

- Physics
- Chemistry
- Biology
- Maths/Stat

I + II + III + IV
COMMON TO ALL

- Language
- Computers
- Humanities

V + VI
PHYSICS GROUP
1 (i + ii + iii + iv)

V + VI
BIOLOGY GROUP
(i + ii + iii + iv + v + vi + vii)

VII, VIII.
i) Biophysics[3]
ii) Biostatistics [3]
iii) Medical Physics.[3]
iv) Bioinformatics [3]

VII, VIII
i) Biochemistry[3]
ii) Biotechnology[3]
iii) Immunology[3]
iv) Genetics[3]
v) Nutrition[3]
vi) Microbiology. [3]
vii) Bioinformatics[3]

IX, X
DESERTATION[3] + OPTIONAL COURSES

1. Those who opt to drop out, or who do not fulfil the prerequisites, may be given the degree of B.Sc. after due evaluation.
2. Provision of switch over from one arm to the other with taking up of deficiency courses.
3. One of the listed areas to be chosen as Major during the VII and VIII semester. The topic of the Dissertation should be in the area of the major.

Figure 2

APPENDIX

1. **The following statements in chapter 1 of the Regulations on Graduate Medical Education, 1997 of MCI are pertinent :-**

' While the curriculum objectives often refer to areas of knowledge of science, they are best taught in a setting of clinical relevance .....' (2.11), and

'.......to encourage integrated teaching ....using a problem based learning approach starting with clinical or community cases and exploring the relevance of various preclinical disciplines in both understanding and resolution of the problem' (2.15).

2. **The following aspects of new biology are included in the curriculum :**

2.1 __Human Anatomy__: Demonstrate knowledge of the basic principles and sequential development of the organs and systems, recognize the critical stages of development and the effects of common teratogens, genetic mutations and environmental hazards. He/she shall be able to explain the developmental basis of the major variations and abnormalities. Understand the principles of karyotyping and identify the gross congenital anomalies.

2.2 __Human Physiology including Bio-physics__

__Lectures:__ (i) Physical principles of transport across cell membranes and across capillary wall.; (ii) Biopotentials; (iii) Physical principles governing flow of blood in heart and blood vessels.

Also physical principles governing flow of air in air passages.

__Practicals:__ Demonstration of: (a) Biopotential of oscilloscope; (b) Electro encephalogram (E.E.G.); (c) Electro Myogram (E.M.G.): (d) Electro Cardiogram (E.C.G.)

2.3 __Biochemistry including Medical Physics and Molecular Biology__

__Goal__ : The broad goal of the teaching of undergraduate students in biochemistry is to make them understand the scientific basis of the life processes at the molecular level and to orient them towards the application of the knowledge acquired in solving clinical problems.

__Objectives__ : At the end of the course, the student shall be able to : (1) Describe the molecular and functional organization of a cell and list its subcellular components; (2) Delineate structure, function and inter-relationships of biomolecules and consequences of deviation from normal; (3) Explain the biochemical basis of inherited disorders; (4) Outline the molecular mechanisms of gene expression and regulation, the principles of genetic engineering and their application in medicine; (5) Summarize the molecular concept of body defenses and their application in medicine; (6) Outline

the biochemical basis of environmental health hazards, biochemical basis of cancer and carcinogenesis; (7) Familiarize with the principles of various conventional and specialized laboratory investigations and instrumentation analysis and interpretation of a given data.

The knowledge acquired in biochemistry shall help the students to integrate molecular events with structure and function of the human body in health and disease.

2.4 <u>Community Medicine</u>

Apply bio-statistical methods and techniques.

Integrative Biology at Undergraduate Level of Science Education

Kambadur Muralidhar[1] and Pramod K Srivastava[2]
[1]Department of Zoology and [2]Center for Science Education & Communication,
University of Delhi, Delhi 110007

The aim of education is development of human consciousness to its full potential. Formal education, spanning a period only a part of our life should catalyse the formation, in students of a mind set which permits self-learning to attain such a level of consciousness. In the present system of formal education, undergraduate college phase is the most important of all phases as it represents the culmination of formal higher education. The masters programme should strictly be geared to pursue research career. The student at the end can either take up a career in pursuit of pure knowledge (teaching and research) or a career to put to use the acquired knowledge in earning a living without adding new basic knowledge.

Modern Science, essentially the post-renaissance European Science has become so pervasive in our day to day life, become so important for national development in every sense of the word that philosophy and science appear to be similar in reach, purpose and method. Biology bridges natural sciences and humanities especially philosophy as the subject ultimately aims to understand living process and living beings.

Biology can be conveniently looked at two levels. One, organismic biology at the level of individual, population and communities answering questions like 'why'? and two, reductionistic biology, at cellular, sub cellular, supramolecular, molecular and sub-molecular levels answering questions like 'How'?

Undergraduate training in biology is in a crisis. One, there appears to be a mismatch between the curricular content and the realistic demands from the biologist of near future. In other words, present curricular content does not do justice to the known dimensions of biology. Two, 21st century has been projected as the century of biology based industrial growth and spectacular achievements have already been registered in bio-technology but our undergraduate biology training does not appear to gear up to produce products with a potential to contribute to such a growth. Three, there is a mushrooming

of computer training centres outside the university system as a short sighted response to changing economy and the consequent flight of students, from universities to 'teaching shops' outside the college system. Four, it is a fact that the 'core capabilities' expected by the general employer to be present in a prospective employee appear to be subject neutral. These are capabilities like updating knowledge independently, analytical thinking and problem solving, communicating knowledge effectively, rational thinking, reflecting and forming opinions, working in multi disciplinary teams, participating in a systematic and responsible work effort etc. Five, science in general and biology in particular has moved towards being multi disciplinary.

Hence, there is a need for integrated biology education at the undergraduate level. The integration should be both with other sciences like physics, chemistry, geology, mathematics, etc. as well as with disciplines of humanities and law. Further, there must be integration between organismic and reductionistic biology. It should also openup and connect to society with regard to employment opportunities and niches. In other words undergraduate training to biology majors should be more broad based in foundation, impart more capabilities in biology and at the same time be flexible and more variable in product profile. These ideas have led to a draft proposal to restructure the B.Sc. level biology course.

The proposed structure has a common module, a main module and a variable module. To provide a broad foundation, the first year course content has to be recast as a common module. A set of compulsory courses designed to project the essence of all science disciplines and to develop abilities of analytical thinking, to learn and use computer science and information technology as a tool and as a medium of learning and communicating biology have to be thought of. Special efforts have to be made to conceptualize the different sciences and to demonstrate the linkages/ interfaces among the different sciences. In other words the common module should present a conceptual account of natural sciences and should lay the strong foundation to develop appreciative level of knowledge in all major science disciplines.

The laboratory exercise part of the common module has to be unconventional in terms of lab design and not constrained by present day 'time tables'. The laboratories, so envisaged, should not replicate individual discipline based laboratories (chemistry lab, biology lab etc.) but should create a new and imaginative learning context. The exercises in the form of small projects should emphasize both basics and applications to other disciplines. This common module laboratory course should enhance the peer learning component and catalyse the establishment of a self learning mind-set. The student should become computer literate, acquire appreciative level of understanding of communicating biology.

The syllabus for biology component of the common module has been framed:

- To bring awareness of the richness of biodiversity i.e. animal and plant resources of our country.
- To demonstrate the validity of reductionism in understanding major areas of biology like physiology.
- To enthuse non-biology stream students by presenting the scope for research from physical and chemical points of view in biology.
- To summarise school level biology in a different perspective.
- To point out the unity among plant, animal and microbial sciences.
- To bring awareness of the application and commercialisation potential of modern biology.

A draft syllabus for the biology component of the common module is given below:

1. Origin, Diversity, and Evolution of life forms: The living world-Chemical Evolution, Origin and Evolution of life forms; speciation; Molecular evolution-concepts and techniques; Diversity of living forms; Biological wealth; Conceptual account of taxonomy and systematics; Conservation biology.
2. Dynamic state of body constituents: Cell as a unit of life; organisation of cells and tissues; cells *in vitro*; Diversity of Biomolecules; Concept of structure-function relationship; Living process as energy utilization process; Nature of free energy in biological systems; metabolic basis of health and disease.
3. Integrative mechanisms in living organisms: Information processing in unicellular and multicellular organisms, Regulatory mechanisms in higher animals and plants; Co-ordinated physiological processes; Adaptation to environmental stresses with selected examples; Genetic basis of living processes.
4. The Living Organism and its environment: Abiotic and biotic components of the environment; Ecological organization; Energy transfers; Elemental cycles.
5. Biotechnology: Biological basis of technologies for production of bioproducts and biopharmaceuticals; reproductive, immuno, protein and gene technologies-concepts and applications; Intellectual Property rights.

The main module should lead to biology honours degree. It should be neither phylogenic group based (botany, zoology, microbiology) nor functional specialized sub-discipline based (Genetics, Biochemistry, Biotechnology). The

course titles should be sub-discipline based, (e.g.: Ecology, Plant Physiology, Developmental Biology, Reproductive Biology, Biochemistry etc). The masters degree programme should be ideally a part of research training and hence should have a set of advanced courses within sub-disciplines (e.g., Regulation of metabolism, structure and function of genes, Fertilization).

The variable module provides the students an opportunity to prepare for a vocation or attempt a specialization. The variable module, unique to each college, should be open to all students. Likely courses could be biotechnology, biophysics, science films, environment assessment, agro chemicals, anthropology, Museum studies, Intellectual Property rights, horticulture, sustainable development, science journalism etc. It is nice to have partners in the design and execution of variable module. The partners could be apart from the college, an industry, a defence organization, an NGO, R & D laboratories of CSIR, ICMR etc. or a University research department. The variable module permits vocationalization. Only those who are serious, motivated and talented can be allowed to move to a research career beginning with integrated Ph.D. programmes.